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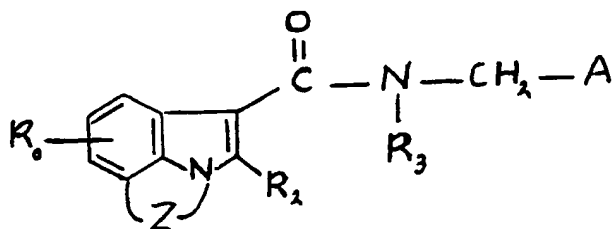
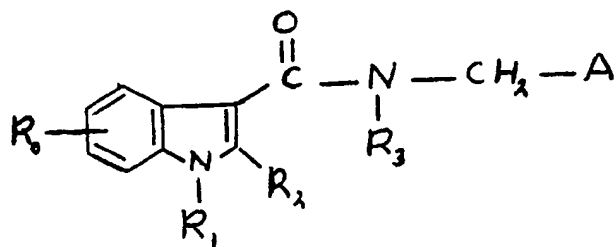
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(54) **New 3-N substituted carbamoyl-indole derivatives.**

(57) The invention relates to a group of new 3-N substituted carbamoyl-indole derivatives of the formula

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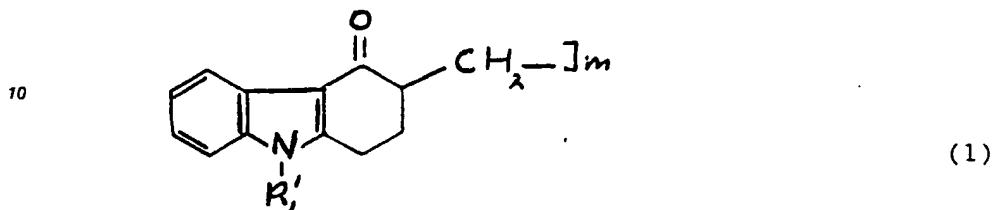


having an antagonistic activity on 5-HT receptors. The compounds can be used for the treatment of symptoms which are caused by excessive stimulation of said receptors in the gastrointestinal system, the central nervous system, the cardiovascular system, the respiratory system, and for alleviating or preventing withdrawal symptoms which are induced by abuse of drugs.

New 3-N substituted carbamoyl-indole derivatives

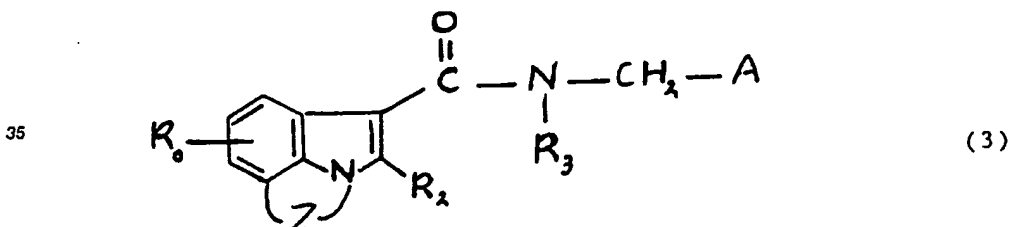
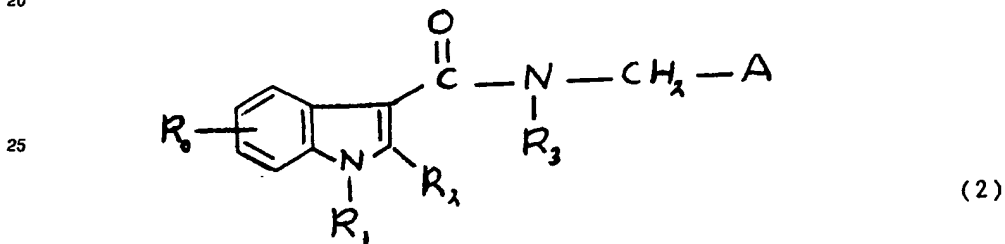
The invention relates to new heterocyclic compounds having an antagonistic activity on 5-hydroxytryptamine (5-HT) receptors, to the preparation thereof and to pharmaceutical compositions comprising such a new compound as an active substance.

British Patent Specification no. 2153821 relates to heterocyclic compounds having an antagonistic activity on 5-HT receptors. These known compounds have the general formula 1



15 wherein R_1' is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, phenylalkyl, and Im is an optionally substituted imidazole radical.

It has been found surprisingly that compounds of formulae 2 and 3



40 wherein

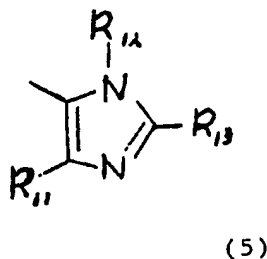
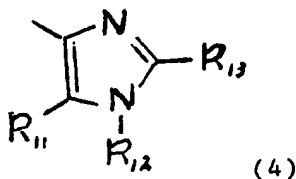
- R_0 is hydrogen, alkyl or alkoxy having 1-4 C-atoms, hydroxy, halogen, trifluormethyl, a group R_6R_7N or R_6R_7N-CO , wherein R_6 and R_7 are hydrogen or alkyl having 1-4 C-atoms or wherein R_6R_7N is a saturated 5- or 6 membered ring,

45 - R_2 and R_3 independently of each other are a hydrogen atom, a branched or non-branched alkyl group having 1-4 C-atoms, alkenyl group having 3-6 C-atoms, cycloalkyl group or benzyl,

- R_1 is hydrogen, 1-8 C alkyl, 3-7 C cycloalkyl, 3-7 C cycloalkyl-(1-4 C)alkyl, 3-6 C alkenyl, 3-8 C alkynyl, phenyl or phenyl-(1-3 C)alkyl, wherein the phenyl group may be substituted, or R_1 is a group $COOR_8$, CO_2R_8 , SO_2R_8 , wherein R_8 is 1-4 C alkyl, 3-7 C cycloalkyl, phenyl or phenyl-(1-2 C)alkyl, or R_1 is a group $R_9R_{10}N$, $C=O$ wherein R_9 and R_{10} independently of each other are hydrogen, 1-4 C alkyl, 3-7 C cycloalkyl, phenyl or phenyl-(1-2 C)alkyl, or wherein R_9 and R_{10} together with the nitrogen atom to which they are bound constitute a saturated 5- or 6 membered ring,

50 - Z together with the carbon atom and the nitrogen atom and the intermediate carbon atom forms a heterocyclic group which consists of 5-8 ring atoms and wherein besides the nitrogen atom already present,

a second hetero atom from the group N, O or S may be present, which ring may be substituted with 1-4 alkyl groups having 1-4 C-atoms, or which ring may be annelated with a saturated or non-saturated carbocyclic or heterocyclic ring, which consists of 5- or 6-ring atoms and which may be substituted,
 - A is a group of formula 4 or 5



wherein one of the groups R_{11} , R_{12} and R_{13} is hydrogen, alkyl having 1-6 C-atoms, cycloalkyl having 3-7 C-atoms, alkenyl having 2-6 C-atoms, and the two other groups independently of each other are hydrogen or alkyl having 1-4 C-atoms,

and the pharmaceutically acceptable acid addition salts thereof have a similar but considerable prolonged activity and a lower toxicity than the known compounds of formula 1.

Suitable acids with which the compounds of formulae 2 and 3 according to the invention can form pharmaceutically acceptable acid addition salts are, for example, hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, and organic acids, for example, citric acid, fumaric acid, maleic acid, tartaric acid, acetic acid, benzoic acid, p-toluenesulphonic acid, methanesulphonic acid and the like.

In the case in which the ring Z is substituted and/or annelated, one or more chiral centres may be present. Both the racemates and the individual enantiomers of compounds of formulae 2 and 3 belong to the invention.

The antagonistic activity of the compounds of formulae 2 and 3 on the 5-HT-induced response was determined and measured in the von Bezold-Jarisch reflex test in rats. The affinity to "neuronal" 5-HT receptors was determined and measured by the displacement of (3 H)GR 38032 F of neuroblastoma cells.

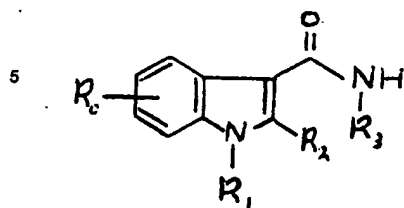
On the basis of the antagonistic activity on this type of 5-HT receptors the compounds may be used for the treatment of symptoms which are caused by overstimulation of the said receptors a) in the gastrointestinal system (nausea and vomiting as a result of exogenous factors, for example, cancer therapy, or endogenous factors, for example, stasis of the stomach and migraine), ulcer, dyspepsia, spasms, irritable bowel syndrome, etc., or b) in the central nervous system (hallucinations, delusions, manias, anxiety, depression, pain, improvement of the vigility, etc.) or c) in the cardiovascular system, for example, spasms of the vessels, arrhythmia, etc., or d) in the respiratory system (including nasal disturbances and disturbances of bronchi and lungs) or e) for relieving withdrawal symptoms which are induced by abuse of drugs.

The compounds according to the invention and their salts can be brought into forms suitable for administration, for example, pills, tablets, coated tablets, capsules, powders, injection liquids and the like by means of techniques conventionally used for this purpose and while using suitable auxiliary substances, for example, solid or liquid carrier materials.

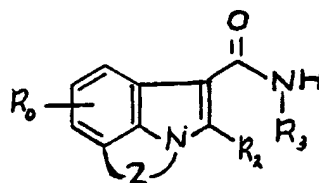
The dosage in which the compounds according to the invention may be used depend on the severity and the nature of the disease to be treated and on the way of administration. As a rule the dosage will be between 0.05 and 20 mg, preferably between 0.1 and 10 mg of active substance daily.

The compounds of formulae 2 and 3, wherein R_0 , R_1 , R_2 , R_3 , Z and A have the meanings mentioned hereinbefore may be prepared in at least one of the following manners:

i) by reaction of a compound of formula 6 or 7

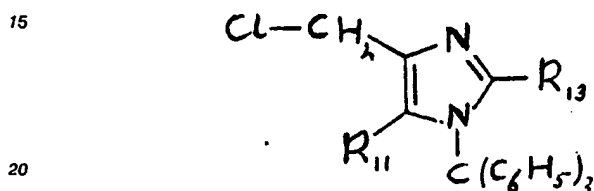


(6)



(7)

wherein R₀, R₁, R₂, R₃, and Z have the above-mentioned meanings, with a compound of formula 8

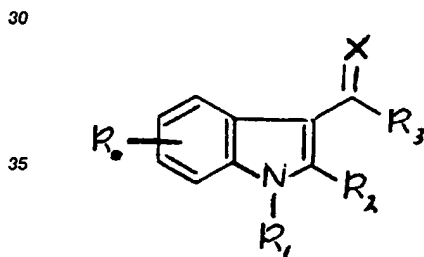


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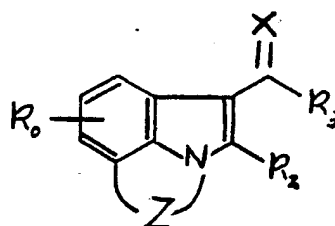
wherein R₁₁ and R₁₃ have the meanings mentioned in formulae 4 and 5, in the presence of potassium hydroxide, preferably in a solvent, for example, dimethyl sulphoxide, dimethyl formamide, etc., succeeded by splitting off the triphenyl methyl group.

The starting compounds of formulae 6 and 7 required for these reactions may be prepared:

a) from the corresponding compounds of formulae 9 and 10



(9)



(10)

wherein X is the group =NOH, by means of the Beckmann reaction, or

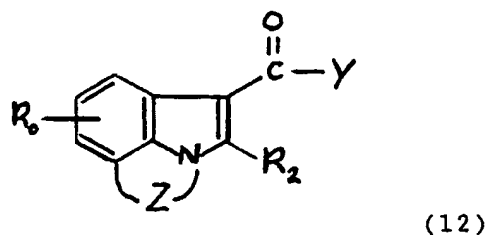
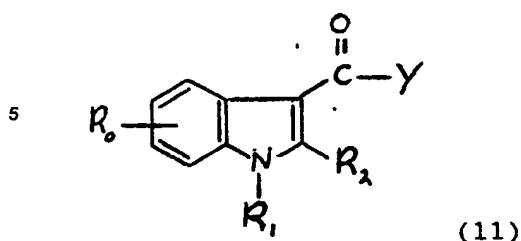
b) from the corresponding compounds of formulae 9 and 10, wherein X is oxygen, by means of the Schmidt reaction.

45 The compounds of formulae 9 and 10, wherein X is the group =NOH, can be prepared in a manner known per se from the analogous compounds of formulae 9 and 10, wherein X is an oxygen atom. The compounds wherein X is oxygen are known compounds or may be prepared in a manner known for analogous compounds.

c) by reaction of a compound of formula 11 or 12

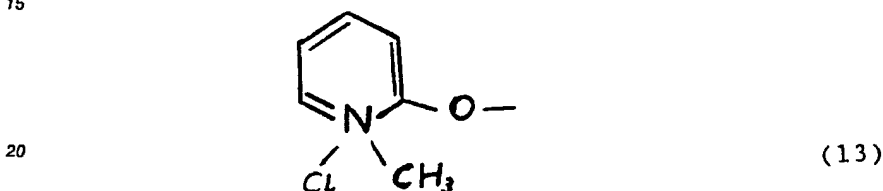
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wherein R_0 , R_1 , R_2 and Z have the meanings mentioned in formulae 2 and 3 and Y is a group which may be replaced by a nucleophile, for example, an alkoxy group, a halogen atom or a group of formula 13

15



with a compound of the formula R_3-NH_2 .

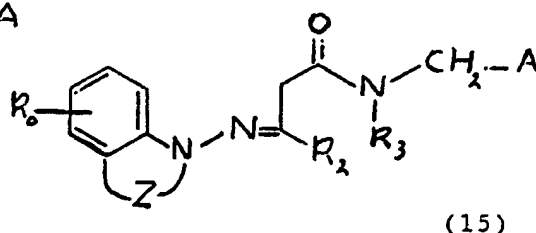
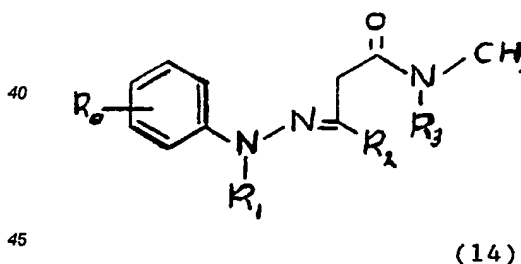
25 The starting compounds of formulae 11 and 12 required for this purpose are known compounds or may be prepared analogously to known compounds. (see EP 0322016)

ii) by metalation of a compound of formula 2 or 3, wherein R_0 , R_1 , R_2 , R_3 , A and Z have the above-mentioned meanings, with the proviso that R_1 and/or R_{12} in formula 2 or R_{12} in formula 3 are a hydrogen atom, and subsequent reaction of the formed metal compound with a compound having formula R_1-Y or $R_{12}-Y$, wherein Y is a group which may be replaced by a nucleophile, for example, a halogen atom. The reaction is preferably carried out in a solvent, for example, dimethylsulphoxide with metalation reagents, for example, sodium hydride, potassium tertiary butoxide, etc.

30 The starting compounds of formulae 2 and 3 required for the said metalation may be obtained, for example, by means of the method described hereinbefore sub i), or by means of the below described methods iii) and iv).

35

iii) by Fischer-indole ring closure of a compound of formula 14 or 15

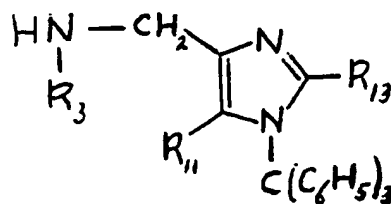


wherein R_0 , R_1 , R_2 , R_3 , A and Z have the meanings mentioned in formulae 2 and 3.

iv) by reaction of a compound of formula 11 or 12 wherein R_0 , R_1 , R_2 , Y and Z have the above mentioned meanings, with a compound of formula 16

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(16)

preferably in an organic solvent, for example, methylene chloride or acetonitrile whether or not in the presence of a base, for example, pyridine or triethyl amine, at temperatures between 0 and 120° C, and then splitting off the trityl group from the formed intermediate product.

The invention will now be elucidated in greater detail with reference to the following examples

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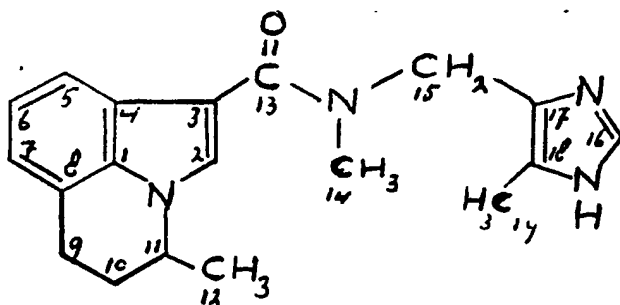
Example I

N-methyl, N-[(5-methyl-1H-imidazol-4-yl)methyl]-4-methyl-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-1-carboxamide .HCl

A mixture of 3.4 g (9.3 mmol) of 5-methyl-4-(methylamino)methyl-1-triphenylmethyl-1H-imidazole, 2.0 g (9.3 mmol) of 4-methyl-5,6-dihydro-4H-pyrrolo[3,2,1-ij] quinoline-1-carboxylic acid, and 2.06 g (10 mmol) of N,N-dicyclohexylcarbodiimide in 100 ml of acetonitrile was stirred for 12 hours under nitrogen. The precipitate was sucked off and the filtrate was evaporated in vacuo. The residue was dissolved in ethyl acetate and washed with 2 N sodium hydroxide and saturated saline respectively, and then evaporated in vacuo. The residue was chromatographed on silicagel using methylene chloride/methanol (95/5) as an eluent. After evaporating the desired fractions 3.6 g of N-methyl, N-[(5-methyl-1-triphenylmethyl-1H-imidazol-4-yl)methyl]-4-methyl-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-1-carboxamide were obtained.

3.2 g (5.67 mmol) of the obtained product was boiled for 30 minutes in a mixture of 33 ml of acetic acid and 33 ml of water, while stirring. The mixture was cooled and diluted with ice-water and sodium hydroxide until weakly alkaline. The mixture was shaken with ethyl acetate. The obtained solution was washed with saline and evaporated in vacuo. The residue was chromatographed on silicagel using methylene chloride/methanol/ammonia(93/7/0.3) as an eluent. The desired fractions were evaporated in vacuo, the residue was dissolved in ethyl acetate and alcoholic hydrochloric acid was added. The solid material was sucked off and dried. 1.0 g of the desired product were obtained.

C-13 nmr (SLV: CDCl₃, ADT: triethylamine, Ref: TMS)

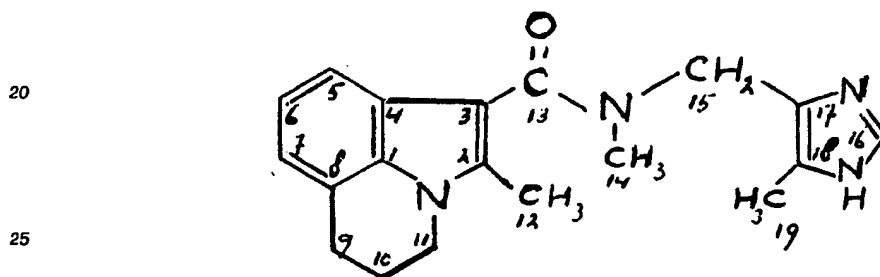


1 133.80 S
2 127.48 D
3 109.97 S
4 124.64 S
5 119.42 D
6 121.20 D
7 118.32 D

8 122.22 S
 9 23.30 T
 10 30.50 T
 11 50.12 D
 5 12 20.48 Q
 13 168.28 S
 14 35.90
 15 43.70
 16 133.55 D
 10 17 128.70
 18 127.48
 19 10.45 Q BROAD LINES FOR CARBONS 14 TO 19

In the same manner were obtained:

15 N-Methyl, N[(5-methyl-1H-imidazol-4-yl)methyl]-2-methyl-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-1-carbox-
 amide hydrochloride



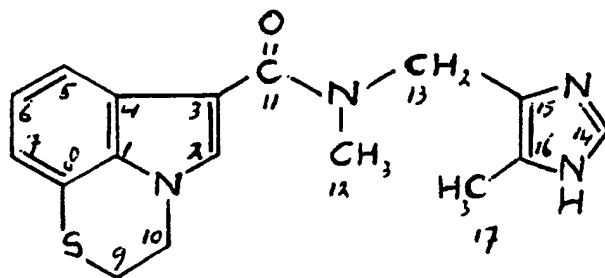
C-13-NMR(SLV: CDCl₃, ADT: Triethylamine, Ref: TMS)

30 1 133.30 S
 2 138.16 S
 3 107.17 S
 4 123.69 S
 5 116.81 D
 35 6 118.65 D
 7 120.77 D
 8 121.68 S
 9 24.56 T
 10 22.70 T
 40 11 41.69 T
 12 11.03 Q
 13 169.45 S
 14 36.60
 15 *.00
 45 16 133.17 D
 17 130.20
 18 125.90
 19 10.55 LINES OF C-ATOMS 14 15 17 18 AND 19 ARE BROAD

C.S. OF C-ATOM 15 IS ABOUT 42 PPM

50 2) N-Methyl,N-[(5-methyl-1H-imidazol-4-yl)methyl]-2,3-dihydro-pyrrolo[1,2,3-de] [1,4]benzothiazine-6-carbox-
 amide C-13-NMR (SLV: CDCl₃, Ref: TMS)

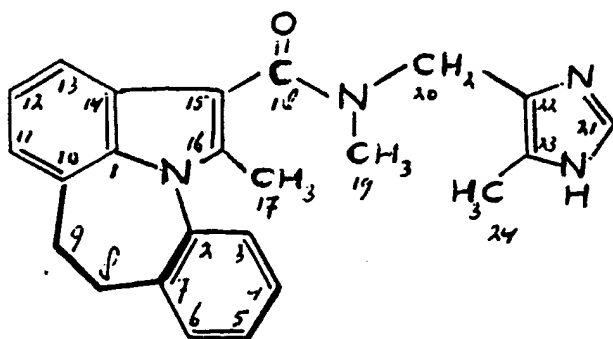
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1	130.14 S
2	129.67 D
3	110.18 S
4	125.48 S
5	117.91 D #
6	119.26 D #
7	121.85 D #
8	117.26 S
9	26.01 T
10	45.99 T
11	167.63 S
12	36.20
13	43.20
14	133.85 D
15	*.00
16	*.00

17 10.70 BROAD LINES FOR CARBONS 11 TO 17

3) N-Methyl, N-[(5-methyl-1H-imidazol-4-yl)methyl]-6,7-dihydro-1-methyl-indolo[1,7a,7-ab] [1]benzazepine-2-carboxamide
C-13-NMR (SLV: CDCl₃, Ref: TMS)

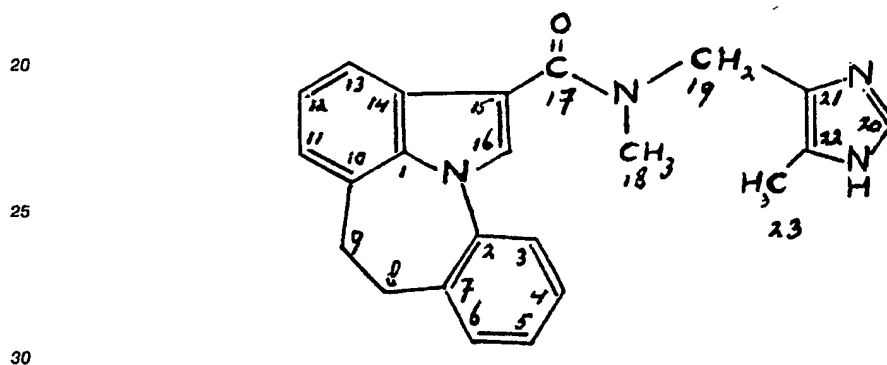


1	135.57 S
2	137.80 S
3	125.67 D
4	126.36 D
5	116.90 D
6	129.88 D
7	137.66 S
8	34.38 T
9	33.95 T
10	126.65
11	126.19 D
12	120.92 D

13 123.38 D
 14 126.94 S
 15 113.90
 16 *.00
 5 17 13.95 Q
 18 169.40
 19 36.67
 20 41.56
 21 133.88
 10 22 *.00
 23 *.00
 24 12.10 CARBONS 15 18 19 20 21 AND 24 ARE VERY BROAD

CARBONS 16 22 AND 23 ARE NOT SHOWN

4) N-Methyl, N-[(5-methyl-1H-imidazol-4-yl)methyl]-6,7-dihydro-indolo[1,7a,7-ab] [1]benzazepine-2-carbox-
 15 amide hydrochloride
 C-13-NMR (SLV: CDCl₃, ADT: Triethylamine, Ref: TMS)

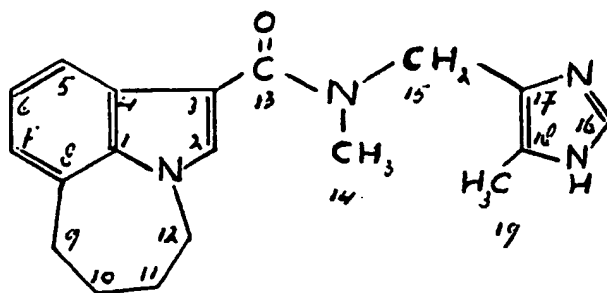


1 134.50 S
 2 139.49 S
 3 125.53 D
 35 4 127.56 D
 5 123.74 D
 6 130.61 D
 7 134.97 S
 8 34.74 T
 40 9 34.20 T
 10 127.65 S
 11 121.19 D
 12 118.92 D
 13 122.42 D
 45 14 128.32 S
 15 113.48 S
 16 128.98 D
 17 167.42 S
 18 *.00
 50 19 *.00
 20 133.89 D
 21 *.00
 22 *.00
 23 10.42 CARBONS 14 16 AND 20 ARE BROAD

55 18 19 21 AND 22 ARE NOT VISIBLE

5) N-Methyl, N-[(5-methyl-1H-imidazol-4-yl)methyl]-4,5,6,7-tetrahydro-pyrrolo[3,2,1-jk] [1]benzazepine-1-carboxamide

C-13-NMR (SLV: CDCl₃, Ref: TMS, ADT TEA)



1	136.34 S
2	131.99 D
3	109.71 S
4	128.15 S
5	118.64 D
6	122.81 D
7	120.96 D
8	127.28 S
9	28.54 T
10	27.04 T
11	33.07 T
12	50.06 T
13	167.77 S
14	35.55
15	43.27
16	133.44 D
17	127.81
18	127.54
19	10.07 Q

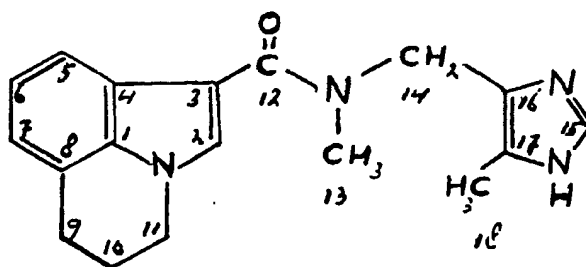
LINES OF C-ATOMS 14 15 17 AND 18 ARE VERY BROAD

Example II

N-methyl, N-[(5-methyl-1H-imidazol-4-yl)methyl]-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-1-carboxamide

1.2 g (6.0 mmol) of 5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-1-carboxylic acid were mixed with 15 ml of thionyl chloride and boiled for 2.5 hours. The excess of thionyl chloride was distilled off in vacuo, and toluene was added. The mixture was evaporated in vacuo again, and the residue was dissolved in 20 ml of acetonitrile. A solution of 2.2 g (6.0 mmol) of 5-methyl-4-(methylamino)methyl-1-triphenylmethyl-1H-imidazole and 1.7 ml (12 mmol) of triethyl amine in 25 ml of acetonitrile was added, the mixture was boiled for 1 hour, and evaporated in vacuo. The residue was shaken with methylene chloride and 2 N NaOH. The organic layer was washed with water and evaporated in vacuo. The residue was chromatographed on silicagel using methylene chloride/methanol (95/5) as an eluent. After evaporating the desired fractions 2.0 g of N-methyl, N-[(5-methyl-1-triphenylmethyl-1H-imidazol-4-yl)methyl]-5,6-dihydro-4H-pyrrolo[3,2,1-ij]-quinoline-1-carboxamide were obtained. This product was treated as described in Example I to remove the triphenylmethyl group, and purified. 0.46 g of the desired title compound were obtained.

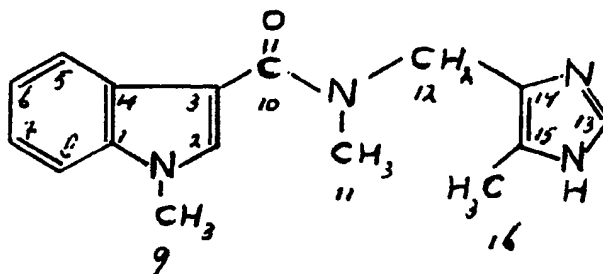
C-13-NMR (SLV: CDCl₃, Ref: TMS):



1	133.92	S
2	129.34	D
3	109.92	S
4	124.37	S
5	118.59	D
6	119.60	D
7	121.53	D
8	122.28	S
9	24.50	T
10	22.76	T
11	44.55	T
12	168.73	S
13	36.68	
14	43.09	
15	133.78	D
16	0.00	
17	125.00	
18	11.47	Q LINES OF C-ATOMS 13 14 16 17 AND 18 ARE BROAD
C.S. OF C-ATOM 16 = CA. 132 PPM		

In the same manner the following compounds were obtained:

1. N-[(5-methyl-1H-imidazol-4-yl)methyl]-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-1-carboxamide; melting point 240 °C (decomposition)
2. N-[(5-methyl-1H-imidazol-4-yl)methyl]-1-methyl-indole-3-carboxamide; melting point 214-219 °C
3. N-methyl, N-[(5-methyl-1H-imidazole-4-yl)methyl]-1-methyl-indole-3-carboxamide C-13-NMR (SLV: CDCl₃, Additive: CH₃OH, Ref: TMS)



1	136.60	S
2	131.94	D +
3	109.25	S
4	126.60	D
5	121.24	D#
6	121.01	D#
7	122.75	D#
8	109.86	D
9	33.20	Q

10 168.47 S

11 36.80

12 42.80

13 133.65 D +

5 14 129.80

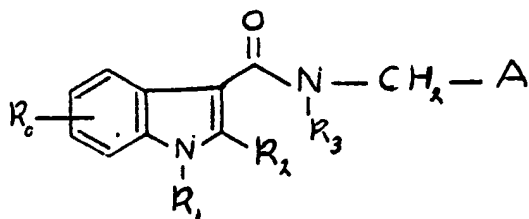
15 125.60

16 10.35 Q MOST LINES ARE BROAD

10 Claims

1. Carbamoyl-indole compounds of formula 2 or 3

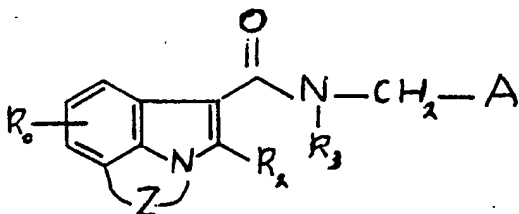
15



20

(2)

25



30

(3)

wherein

- R_6 is hydrogen, alkyl or alkoxy having 1-4 C-atoms, hydroxy, halogen, trifluormethyl, a group R_6R_7N or R_6R_7N-CO , wherein R_6 and R_7 are hydrogen or alkyl having 1-4 C-atoms or wherein R_6R_7N is a saturated 5- or 6 membered ring,

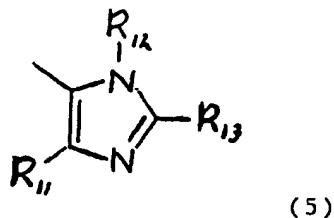
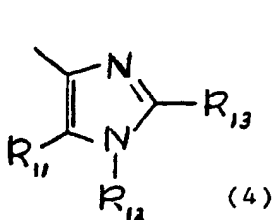
- R_2 and R_3 independently of each other are a hydrogen atom, a branched or non-branched alkyl group having 1-4 C-atoms, alkenyl group having 3-6 C-atoms, cycloalkyl group or benzyl,

- R_1 is hydrogen, 1-8 C alkyl, 3-7 C cycloalkyl, 3-7 C cycloalkyl-(1-4 C)alkyl, 3-6 C alkenyl, 3-8 C alkynyl, phenyl or phenyl-(1-3 C)alkyl, wherein the phenyl group may be substituted, or R_1 is a group $COOR_8$, COR_8 , SO_2R_8 , wherein R_8 is 1-4 C alkyl, 3-7 C cycloalkyl, phenyl or phenyl-(1-2 C)alkyl, or R_1 is a group $R_9R_{10}N-C(=O)-$ wherein R_9 and R_{10} independently of each other are hydrogen, 1-4 C alkyl, 3-7 C cycloalkyl, phenyl or phenyl(1-2 C)alkyl, or wherein R_9 and R_{10} together with the nitrogen atom to which they are bound constitute a saturated 5- or 6 membered ring,

- Z together with the carbon atom and the nitrogen atom and the intermediate carbon atom forms a heterocyclic group which consists of 5-8 ring atoms and wherein besides the nitrogen atom already present, a second hetero atom from the group N, O or S may be present, which ring may be substituted with 1-4 alkyl groups having 1-4 C-atoms, or which ring may be annelated with a saturated or non-saturated carbocyclic or heterocyclic ring, which consists of 5- or 6-ring atoms and which may be substituted,

- A is a group of formula 4 or 5

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wherein one of the groups R_{11} , R_{12} and R_{13} is hydrogen, alkyl having 1-6 C-atoms, cycloalkyl having 3-7 C-atoms, alkenyl having 2-6 C-atoms, and the two other groups independently of each other are hydrogen or alkyl having 1-4 C-atoms, and the pharmaceutically acceptable acid addition salts thereof.

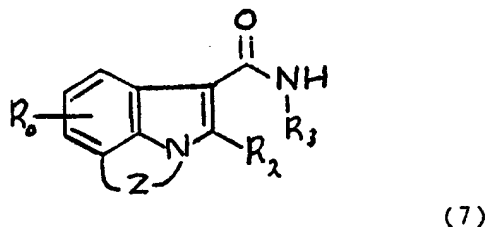
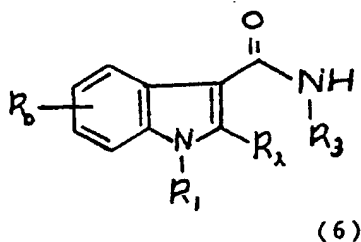
2. Pharmaceutical compositions which comprise as the active substance a carbamoyl-indole compound, characterised in that they comprise at least one compound as claimed in Claim 1 as an active substance.

3. A method of preparing pharmaceutical compositions by bringing an active substance into a form suitable for administration, characterised in that at least one compound as claimed in Claim 1 is used as an active substance.

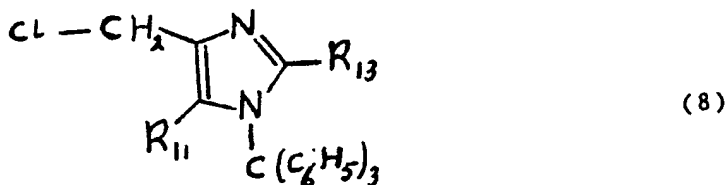
4. A method of treating symptoms which are caused by overstimulation of 5-hydroxytryptamine receptors, characterised in that a compound as claimed in Claim 1 is used.

5. A method of preparing carbamoyl-indole compounds, characterised in that compounds of formula 2 or 3 are prepared by

a) reaction of a compound of formula 6 or 7



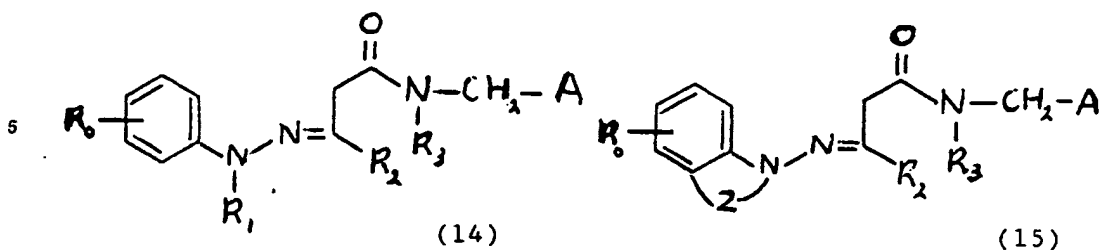
with a compound of formula 8



in which formula R_0 , R_1 , R_2 , R_3 , Z , R_{11} , and R_{13} have the meanings mentioned in Claim 1, or

b) metalation of a compound of formula 2 or 3, wherein R_1 and/or R_{12} represent(s) hydrogen, succeeded by reaction with a compound of formula $R_1\text{-Y}$ or $R_{12}\text{-Y}$, wherein Y is a group which may be replaced by a nucleophile, or

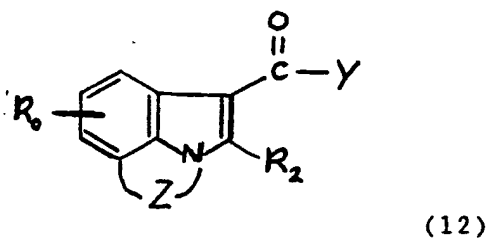
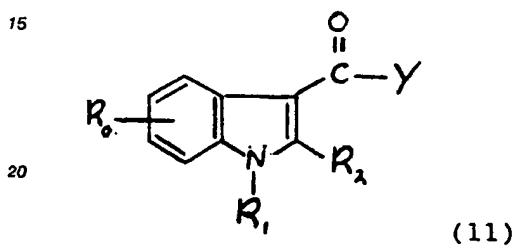
c) Fischer-indole ring closure of a compound of formula 14 or 15



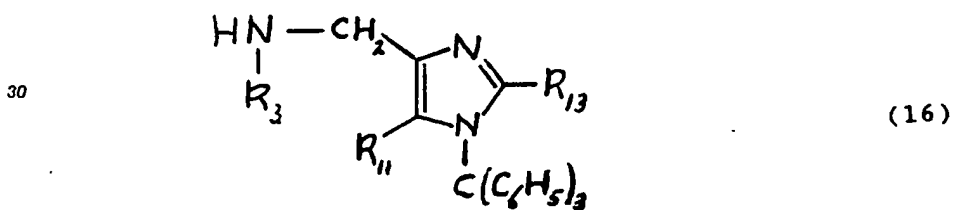
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wherein R_0 , R_1 , R_2 , R_3 , A and Z have the meanings given in claim 1, or
d) reaction of a compound having formula 11 or 12

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25 with a compound having formula 16



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in which formula the symbols have the meaning given in claim 1, followed by splitting off the protective trityl group.

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(54) **New 3-N substituted carbamoyl-indole derivatives.**

(57) The invention relates to a group of new 3-N substituted carbamoyl-indole derivatives of the formula

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Application number

EP 90 20 0908

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	EP-A-0 306 323 (GLAXO) * Claims 1,16 *	1,2	C 07 D 471/06 C 07 D 513/06 C 07 D 487/06 C 07 D 403/12 A 61 K 31/435 A 61 K 31/54 A 61 K 31/55 A 61 K 31/415//
A	EP-A-0 297 651 (DUPHAR) * Claim 1; page 2, lines 7-20 *	1,2	(C 07 D 471/06 C 07 D 221/00 C 07 D 209/00)
P,X	EP-A-0 347 229 (GLAXO) * Claim 1; page 4, lines 41-52 *	1,2	(C 07 D 513/06 C 07 D 279/00 C 07 D 209/00 (C 07 D 487/06 C 07 D 223/00 C 07 D 209/00)
E	EP-A-0 403 261 (GLAXO)		
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 D 471/00 C 07 D 487/00 C 07 D 513/00 C 07 D 403/00 A 61 K 31/00
INCOMPLETE SEARCH			
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.</p> <p>Claims searched completely: 1-3,5 Claims searched incompletely: Claims not searched: 4 Reason for the limitation of the search:</p> <p>Method for treatment of the human or animal body by surgery or therapy (See art. 52(4) of the European Patent Convention)</p>			
Place of search THE HAGUE		Date of completion of the search 11-07-1991	Examiner ALFARO
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